SHOCK, Vol. 43, No. 6, pp. 549–555, 2015

IMPROVING THE PREDICTION OF MORTALITY AND THE NEED FOR LIFE-SAVING INTERVENTIONS IN TRAUMA PATIENTS USING STANDARD VITAL SIGNS WITH HEART-RATE VARIABILITY AND COMPLEXITY

Nehemiah T. Liu,* John B. Holcomb,† Charles E. Wade,† and Jose Salinas*

**US Army Institute of Surgical Research, Fort Sam Houston, Texas; and †Center for Translational Injury Research, Department of Surgery, University of Texas Health Science Center at Houston, Houston, Texas*

Received 14 Jan 2015; first review completed 2 Feb 2015; accepted in final form 9 Feb 2015

ABSTRACT—The goal of this study was to determine the effectiveness of using traditional and new vital signs (heart rate variability and complexity [HRV, HRC]) for predicting mortality and the need for life-saving interventions (LSIs) in prehospital trauma patients. Our hypothesis was that statistical regression models using traditional and new vital signs would be superior in predictive performance over models using standard vital signs alone. This study involved 108 prehospital trauma patients transported from the point of injury via helicopter. Heart rate variability and HRC were calculated using criterion standard R-R interval sequences manually verified from the patients' electrocardiograms. Means and standard deviations for vital signs, HRV, HRC, and Glasgow coma scale (GCS) scores were obtained for nonsurvivors versus survivors and LSI versus non-LSI patient groups and then compared using Wilcoxon statistical tests. Receiver-operating characteristic curves were also obtained to compare different regression models for predicting mortality and the need for LSIs. Seventeen patients (16%) died. Eighty-two patients (76%) received a total of 142 LSIs. Receiver-operating characteristic curves demonstrated better prediction of mortality and LSI needs using heart rate and HRC (area under the curve [AUC]; AUCs, 0.86 and 0.86) than using heart rate alone (AUCs, 0.79 and 0.57). Likewise, receiver-operating characteristic curves demonstrated better prediction using total GCS score and HRC (AUCs, 0.82 and 0.97) than using total GCS score (AUCs, 0.81 and 0.91). Similar results were obtained for heart rate and HRV (AUCs, 0.86 and 0.73). The major implication of this study was that traditional and new vital signs (HRV and HRC) should be used simultaneously to improve prediction of mortality and the need for LSIs in prehospital trauma patients during all echelons of trauma care. Improvements in the timely use and diagnostic accuracy of transportable vital signs monitors will require use of traditional and new vital signs from the trauma patient cohort.

KEYWORDS—Mortality, life-saving interventions, heart rate complexity, heart rate variability, trauma

INTRODUCTION

Initiation of early and effective life-saving interventions (LSIs) is an important aspect of trauma medicine, especially in the prehospital and battlefield settings. In these environments, potential delays in administering LSIs could lead to increased morbidity and mortality after trauma (1, 2). Traditionally, medics have relied on standard vital signs such as blood pressure and heart rate (HR) to monitor trauma patients for abrupt changes that indicate the need for LSIs. Unfortunately, there are limitations inherent in monitoring traditional vital signs that could possibly prevent the medic's ability to identify patient destabilization until late and irreversible changes in state take place (1, 3–7). Because monitoring of standard vital signs has become routine throughout the spectrum of critical care, earlier administration of LSIs implies a need for improvements in the timely use and diagnostic accuracy of vital signs monitors (1, 2, 8).

Address reprint requests to Nehemiah T. Liu, MS, US Army Institute of Surgical Research, 3698 Chambers Pass, JBSA Fort Sam Houston, Texas 78234-6315. E-mail: nehemiah.liu@us.army.mil.

This work was supported by the National Trauma Institute, the Combat Casualty Care Research Program, and the State of Texas Emerging Technology Fund.

Disclaimers: This study was conducted under a protocol reviewed and approved by the University of Texas Health Science Center at Houston and in accordance with the approved protocol. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

DOI: 10.1097/SHK.0000000000000356

One possible solution for improving LSI performance via monitoring may be the use of new vital signs such as advanced indices derived from the electrocardiogram (ECG), namely, HR variability (HRV) and complexity (HRC), which are capable of detecting subtle changes in HR behavior driven by the autonomic nervous system, which could precede changes in standard vital signs (9–13). These indices could be integrated into existing vital signs monitors without adding new sensors and/or boxes to the medic's kit. Previous studies have shown the predictive power of HRV and HRC for risk stratification, diagnosis, and continuous monitoring of traumatically injured patients (14). Benefits of using HRV and HRC include their ease for rapid calculation, noninvasive nature, and robustness against certain kinds of noise (15, 16).

However, as standard vital signs alone may not be reliable in many situations, HRV and HRC have several significant drawbacks, including limited use in the presence of high artificial noise levels and ectopic beats in the captured waveforms (14–17). Recent work suggests that new vital signs such as HRV and HRC should be used in conjunction with traditional vital signs to achieve more accurate diagnostic capabilities (2). In light of this work, the objectives of this study were 1) to confirm that HRV and HRC can discriminate between nonsurvivors and survivors of trauma and 2) between trauma patients who received one or more LSIs and those who received none; and 3) to compare different multivariate logistic regression models for predicting mortality and 4) for predicting the need for LSIs in trauma patients. Our hypothesis

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE **01 JUN 2015**	2. REPORT TYPE **N/A**	3. DATES COVERED **-**

4. TITLE AND SUBTITLE **Improving the Prediction of Mortality and the Need for Life-Saving Interventions in Trauma Patients Using Standard Vital Signs With Heart-Rate Variability and Complexity**	5a. CONTRACT NUMBER 5b. GRANT NUMBER 5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S) **Liu, Nehemiah T.; Holcomb, John B.; Wade, Charles E.; Salinas, Jose;**	5d. PROJECT NUMBER 5e. TASK NUMBER 5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **United States Army Institute of Surgical Research, JBSA Fort Sam Houston, Tx 78234**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S) 11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**	**SAR**	**8**	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std Z39-18

was that models incorporating traditional and new vital signs to predict mortality and the need for LSIs would be able to outperform models incorporating only traditional vital signs.

MATERIALS AND METHODS

Subjects and protocol

This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol. After approval, 108 prehospital patient records were selected from the US Army Institute of Surgical Research Trauma Vitals (TV) database based on availability of: 1 - vital signs data; 2 - ECG waveforms; and 3 -manual verification of all R-to-R interval (RRI) sequences. Because all data were analyzed *post hoc*, the study was considered minimal risk, and informed patient consent was waived.

The cohort used in this study consisted of prehospital trauma patients with blunt and penetrating injuries transported from the point of injury by helicopter service to a level I trauma center in Houston, Texas or San Antonio, Texas. All patients were monitored during transport using a Welch Allyn PIC 50 (Welch Allyn, Skaneateles Falls, NY) monitor. Data from a personal digital assistant and flash cards attached to the monitor were extracted by research personnel and uploaded to the TV database for analysis. All nonelectronic data were manually recorded on the run sheet from the monitor's screen by Emergency Medical Services medics, then collected on a standardized form and entered into the TV database. These included demographic data, physical examination results, Glasgow Coma Scale (GCS) scores, and interventions performed on the patients in the field. Life-saving interventions consisted of endotracheal intubations, transfusions, tube thoracostomies, cardiopulmonary resuscitations, needle decompressions, angioembolizations, cricothyrotomies, thoracotomies, and cardioversions.

Importantly, numeric data were stored at a rate of 1 measurement every 3 min, coinciding with the patient's noninvasive blood pressure measurements, whereas waveform data were stored at a rate of 375 Hz. Of the 108 waveforms, 17 ECGs (16%) belonged to nonsurvivors, whereas 91 ECGs belonged to survivors of trauma. In addition, 82 ECGs (76%) belonged to patients who received at least one LSI, whereas the remaining 26 ECGs (24%) belonged to patients who received none. Lengths of patients' ECGs varied from approximately 15 to 20 min. Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), blood oxygenation (SpO_2), shock index (SI = HR/SBP), and pulse pressure (PP = SBP – DBP) were also captured during trauma care for patient assessment.

Heart rate variability and complexity

For this study, HRV and HRC were derived using true RRI sequences extracted from the patients' ECG waveforms. The criterion standard for obtaining true RRI sequences was manual verification of R waves, which was accomplished by importing the ECG waveform data into WinCPRS software (Absolute Aliens Oy, Turku, Finland), visually analyzing the data, and marking times and positions of all R waves. An HRV ratio was computed using the Poincaré variability ratio, SD1/SD2, which describes the short-term and long-term RRI variability of a sequence. This ratio was selected owing to its suitability for analysis of shorter time series and frequent citations in literature. SD1 and SD2 were obtained from the following equations:

$$SD1^2 = \quad \mathrm{var}\left(\frac{1}{\sqrt{2}}RRI_i - \frac{1}{\sqrt{2}}RRI_{i+1}\right) = \frac{1}{2}SDSD^2 , \qquad 1$$

and

$$SD2^2 = 2SDRR^2 - \frac{1}{2}SDSD^2 , \qquad 2$$

$\forall i = 1, \ldots, N$, where var(•) denotes the variance function, SDRR denotes the standard deviation of RRIs, SDSD denotes the standard deviation of successive RRI differences, and N denotes the number of RRIs in the sequence window (18). An HRC value was computed via the method of sample entropy, SampEn (m, r, N), which describes the conditional probability that 2 epochs similar for m RRIs remain similar at the next RRI, i.e., differ by no more than some tolerance r (in milliseconds) (19). Parametric values (N = 200, m = 2, r = 6) were established from previous work (2, 12, 16, 17). In addition, the following equations were used to calculate SampEn:

$$\mathrm{SampEn}(m,r,N) = -\ \ln\ (A/B)\ , \qquad 3$$

$$B = [(N-m-1)/2]\textstyle\sum_{i=1}^{N-m} B_i^r(m)\ , \qquad 4$$

$$A = [(N-m-1)/2]\textstyle\sum_{i=1}^{N-m} A_i^r(m)\ . \qquad 5$$

Here, $x_m(i)$ denotes a segment of m consecutive RRIs starting at index i and running from $i = 1, \ldots, N - m$, $B^r{}_i(m)$ denotes the number of epochs $x_m(j)$ within r of $x_m(i)$, for $i \neq j$, multiplied by $(N - m - 1)^{-1}$, and $A^r{}_i(m)$ denotes the number of epochs $x_{m+1}(j)$ within r of $x_{m+1}(i)$, for $i \neq j$, multiplied by $(N - m - 1)^{-1}$ (19).

Statistical analyses

Like the statistical analyses described in (2), all data sets were analyzed using Wilcoxon tests for nonparametric distributions. Data were expressed as means ± SD. The power of demographics, vital signs, HRV, HRC, and GCS scores to identify nonsurvivors and whether LSIs were performed was estimated using multivariate logistic regression modeling. In other words, initial multivariate logistic regression analyses were done for all subjects with independent variables of age, height, race, and weight and with dependent variables of HR, SBP, DBP, MAP, RR, and SI. These analyses excluded HRV and HRC values. Factors that were not significant ($P > 0.05$) were removed from the model via backward elimination. A second set of analyses was done for dependent variables of HR, SBP, DBP, MAP, RR, and SI, including HRV and HRC for performance comparisons with the initial set. In addition, a third set and a fourth set of analyses were performed for all subjects to include GCS scores, with and without HRV and HRC as dependent variables, respectively. The ability of statistical models to predict mortality and the need for at least one LSI was assessed using sensitivity and specificity scores as well as receiver-operating characteristic (ROC) curves. Statistical analyses were performed using JMP version 9.0.0 (SAS Institute, Cary, NC) and the R Language (http://www.r-project.org/).

RESULTS

Patients' demographics for 108 patients are tabulated in Table 1, whereas interventions performed on these patients and classified as life saving by a multidisciplinary team of trauma

Table 1. **Demographics of patients (n = 108)**

Characteristics	Mean ± SD or n (%)
Age, yrs	37 ± 14
Sex	
Male	82 (76)
Female	25 (23)
Not recorded	1 (1)
Race	
White	44 (41)
Black	6 (6)
Hispanic	24 (22)
Asian/Pacific	3 (3)
Not recorded	31 (28)
Mechanism of injury	
Blunt	93 (86)
Penetrating	13 (12)
Not recorded	2 (2)
Receiving LSI(s)	82 (76)
Died	17 (16)
Injury severity score	17 ± 11
Total GCS score	9 ± 5
Field HR,* beats per minute	106 ± 27
Field SBP,* mm Hg	116 ± 23
Field DBP,* mm Hg	79 ± 16
ED HR,* beats per minute	98 ± 25
ED SBP,* mm Hg	114 ± 27
ED DBP,* mm Hg	75 ± 21

*Denotes entry values taken from the run sheet.
SD, standard deviation; WVSM, wireless vital signs monitor; ED, emergency department.

TABLE 2. **Life-saving interventions**

Life-saving interventions	# n	% n/142
Prehospital	87	61
Emergency department	55	39
Angioembolization	1	1
Blood	30	21
Cardiopulmonary resuscitation	9	6
Chest tube	18	13
Intubation	73	51
Needle decompression	8	6
Surgical cricothyrotomy	2	1
Thoracotomy	1	1
Total	142	100

experts are listed in Table 2. Of these 108 patients, 17 (16%) died, of which 16 (15%) required an LSI. Of the 108 patients, 26 (24%) did not require an LSI. The other 82 (76%) patients received a total of 142 LSIs. Eighty-seven (61%) of the LSIs were performed prehospital and 55 (39%) in the emergency room. Interventions consisted of the following: 73 endotracheal intubations, 30 transfusions, 18 tube thoracostomies, 9 cardiopulmonary resuscitations, 8 needle decompressions, 1 angioembolization, 2 cricothyrotomies, and 1 thoracotomy. Importantly, the demographics of the chosen population included HRs ranging from 20 to 156 beats per minute, SBPs ranging from 80 to 170 mm Hg, DBPs ranging from 44 to 110 mm Hg, and various types of injuries and LSIs. This cohort provided the ECG morphology for HRV and HRC calculations.

Means of HRV and HRC statistics, SDs, and P values obtained via Wilcoxon tests for nonsurviving (NS) versus surviving (S) patient groups and for LSI versus non-LSI (NLSI) patient groups are shown in Tables 3 and 4, respectively. These tables were used to confirm that HRV and HRC can discriminate between the different patient groups, respectively. Heart rate variability (Poincaré) ratios were consistent with the fact that a higher ratio, i.e., a decreasing long-term variability SD2, is associated with increasing risk of mortality and the need for an LSI (2, 14). However, only maximum HRV ratios for NS patients in Table 3 were statistically larger ($P < 0.05$) than ratios for S patients. Heart rate complexity (SampEn) values for patients who received at least one LSI were consistent with the fact that this group often has lower HRC than NLSI patients (2, 14). Only minimum HRC values for NS patients in Table 3 were statistically smaller than the values for S patients.

For the multivariate logistic regression models in Table 5, results showed that increasing mean HR was associated with an increased risk for mortality. Age, height, race, and weight were removed from the final models via backward elimination because they were not significantly associated with mortality. In the model for vital signs alone (Table 5), the odds ratio was 1.04 (95% confidence interval [CI], 1.01–1.09; $P = 0.007$) for mean HR (per beats per minute increase). Importantly, inclusion of HRC in the multivariate logistic regression analyses showed that decreasing minimum HRC was also associated with an increased risk for mortality, increasing odds by 100%. Here, odds ratios were 1.05 (95% CI, 1.01–1.09; $P = 0.007$) for mean HR (per beats per minute increase) and 0.01 (95% CI, 0.00–0.58; $P = 0.02$) for minimum HRC (per unit increase).

On the other hand, for the regression models in Table 6, no traditional vital signs were significantly associated with an increased risk for LSIs. Again, age, height, race, and weight were removed from the final models via backward elimination because they were not significantly associated with LSIs. In the model for vital signs alone (Table 6), the odds ratio was 1.01 (95% CI, 0.99–1.04; $P = 0.21$) for mean HR (per beats per minute increase). Inclusion of HRC in the regression analyses again showed that decreasing minimum HRC was associated with an increased risk for LSIs and increased odds by nearly 100%. The odds ratio was 0.02 (95% CI, 0.00–0.14; $P < 0.0001$) for minimum HRC (per unit increase).

When total GCS scores were included in the models, no traditional vital signs were significantly associated with an

TABLE 3. **Comparison of HRV and HRC values between patient groups for mortality**

	NS patients (n = 17)		S patients (n = 91)		
Measure	Mean	SD	Mean	SD	P
Mean HRV ratio	0.395	0.198	0.339	0.208	0.228
Maximum HRV ratio	0.927	0.427	0.713	0.421	0.063
Minimum HRV ratio	0.165	0.146	0.138	0.072	0.787
Mean HRC	0.886	0.343	1.000	0.310	0.154
Maximum HRC	1.549	0.481	1.591	0.382	0.524
Minimum HRC	0.274	0.275	0.451	0.348	0.030

SD, standard deviation.

TABLE 4. **Comparison of HRV and HRC values between patient groups for LSIs**

	LSI patients (n = 82)		NLSI patients (n = 26)		
Measure	Mean	SD	Mean	SD	P
Mean HRV ratio	0.364	0.230	0.298	0.091	0.036
Maximum HRV ratio	0.811	0.454	0.545	0.239	<0.001
Minimum HRV ratio	0.133	0.094	0.172	0.054	0.011
Mean HRC	0.908	0.290	1.217	0.287	<0.001
Maximum HRC	1.535	0.391	1.743	0.380	<0.001
Minimum HRC	0.321	0.281	0.744	0.324	<0.001

TABLE 5. **Logistic regression models with various risk factors (excluding GCS) for mortality**

Variable	Odds ratio for mortality (95% CI)*	P
Field HR	1.04 (1.01–1.09)	0.007
With HRC		
Field HR	1.05 (1.01–1.09)	0.007
Minimum HRC	0.01 (0.00–0.58)	0.02

*Odds ratios for measurements reflect per-unit increase.

Table 6. **Logistic regression models with various risk factors (excluding GCS) for LSIs**

Variable	Odds ratio for LSIs (95% CI)*	*P*
Field HR	1.01 (0.99–1.04)	0.21
With HRC		
Field HR	1.00 (0.98–1.03)	0.86
Minimum HRC	0.02 (0.00–0.14)	<0.0001

*Odds ratios for measurements reflect per-unit increase

Table 8. **Logistic regression models with various risk factors (including GCS) for LSIs**

Variable	Odds ratio for LSIs (95% CI)*	*P*
Total GCS score	0.41 (0.13–0.66)	<0.0001
With HRC		
Total GCS score	0.29 (0.04–0.63)	<0.0001
Minimum HRC	0.01 (0.00–0.10)	<0.0001

*Odds ratios for measurements reflect per-unit increase.

increased risk for mortality or LSIs. However, inclusion of HRC in the multivariate logistic regression analyses showed that decreasing minimum HRC was also associated with an increased risk for mortality or LSIs and could be used for risk stratification. Odds ratios for regression models with various risk factors (including GCS scores) for mortality and LSIs are shown in Tables 7 and 8, respectively.

Receiver-operating characteristic curves (Figs. 1 and 2) demonstrated better prediction for mortality and LSIs using HR and HRC (area under the curve [AUC]; AUCs, 0.86 and 0.86, respectively) than using HR alone (AUCs, 0.79 and 0.57, respectively). Likewise, ROC curves (Figs. 3 and 4) demonstrated better prediction for mortality and LSIs using total GCS score and HRC (AUCs, 0.82 and 0.97, respectively) than using total GCS score alone (AUCs, 0.81 and 0.91, respectively).

DISCUSSION

This study investigated the effectiveness of using traditional and new vital signs for predicting mortality and the need for LSIs in prehospital trauma patients through different comparisons of statistical models, ROC curves, and AUC results. It was the first to use a multivariate logistic regression model to determine whether standard vital signs along with HRV and HRC were better in predicting mortality than standard vital signs alone. In the statistical analyses previously described, HR generally increased the odds of death or an LSI by no more than 5%. When HRC values were included in the analyses, they increased the odds of death and the need to perform LSIs by approximately 100%. When GCS scores were included in the analyses, HRC continued to increase the odds of death and the need for an LSI by 100%. Following recent work described in Liu et al. (2), this study confirmed that models using both traditional and new vital signs were superior over models using only traditional vital signs for predicting the need for LSIs in trauma patients. Furthermore, this study confirmed that models using both traditional and new vital signs were superior over models using only traditional vital signs for predicting mortality in trauma patients. The major implication of this study was that traditional and new vital signs should be used simultaneously to improve prediction of mortality and the need for LSIs in prehospital trauma patients during all echelons of trauma care. Again, this study demonstrated that multivariate logistic regression models incorporating HRV and HRC could increase the mortality and LSI prediction accuracy for trauma cohorts.

Although values and significances of odds ratios were smaller than those described in Liu et al. (2) (most likely owing to the number of LSI patients versus NLSI patients), this study provided a different cohort to validate the hypothesis and results presented in Liu et al. (2). It is important to note that this study and previous work (2) involved 2 different databases containing disparate sets of patients, yet both studies were able to demonstrate the power of vital signs and HRC to predict the need for LSIs in prehospital trauma patients. A novelty of this study was the exploration of traditional and new vital signs for predicating mortality, showing that a multivariate logistic regression model combining HR and HRC was superior in performance over a model using HR. Unlike the methodology described in Liu et al.

Table 7. **Logistic regression models with various risk factors (including GCS) for mortality**

Variable	Odds Ratio for Mortality (95% CI)*	*P*
Total GCS score	0.77 (0.62–0.90)	0.001
With HRC		
Total GCS score	0.79 (0.63–0.93)	0.003
Minimum HRC	0.20 (0.01–1.98)	0.18

*Odds ratios for measurements reflect per-unit increase.

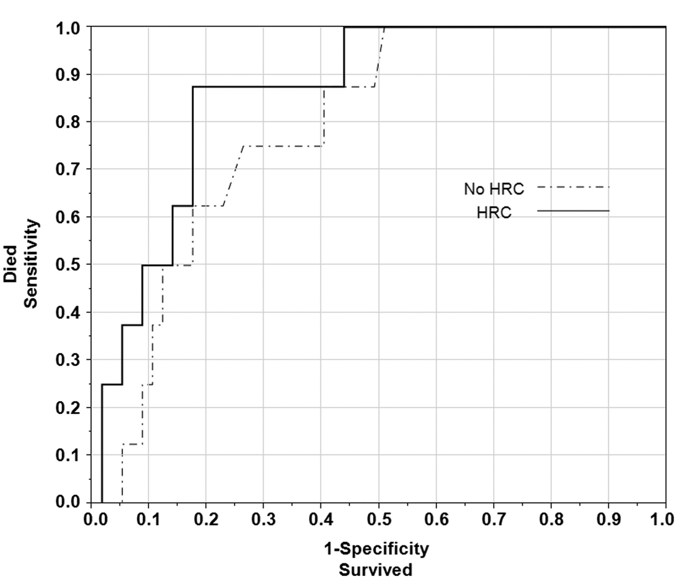

Fig. 1. **Receiver-operating characteristic curves for models predicting mortality (excluding GCS scores)**. Receiver-operating characteristic curves were obtained to examine the discriminating power of multivariate logistic regression models (excluding GCS scores) for the outcome of mortality in 108 subjects. The curves demonstrated better mortality prediction for models using both vital signs and HRC (AUC, 0.86) than for models using only vital signs (AUC, 0.79).

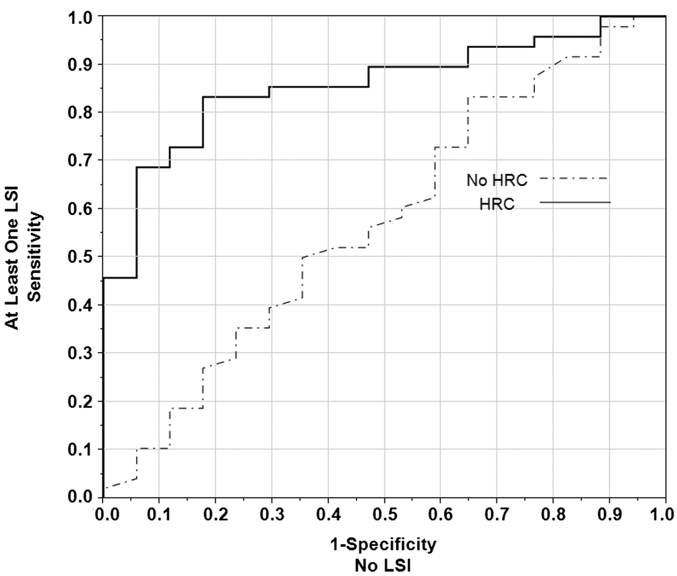

FIG. 2. **Receiver-operating characteristic curves for models predicting interventions (excluding GCS scores)**. Receiver-operating characteristic curves were obtained to examine the discriminating power of multivariate logistic regression models (excluding GCS scores) for the outcome of at least one LSI in 108 subjects. The curves demonstrated better LSI prediction for models using both vital signs and HRC (AUC, 0.86) than for models using only vital signs (AUC, 0.57).

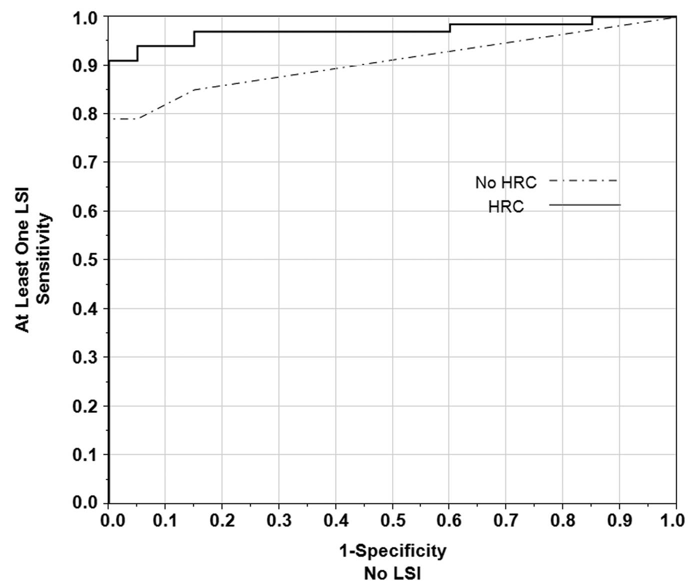

FIG. 4. **Receiver-operating characteristic curves for models predicting interventions (including GCS scores)**. Receiver-operating characteristic curves were obtained to examine the discriminating power of multivariate logistic regression models (including GCS scores) for the outcome of at least one LSI in 108 subjects. The curves demonstrated better LSI prediction for models using vital signs, GCS scores, and HRC (AUC, 0.97) than for models using only GCS scores (AUC, 0.91).

(2), HRV was calculated via the Poincaré ratio (see *Heart-Rate Variability and Complexity*). Moreover, HRV and HRC were retrospectively derived from the patients' ECG waveforms rather than extracted from the vital signs monitor. Owing to previous work (2) and the power of HRC for group discrimination, Tables 1 through 4 only showed results involving HRC rather than HRV (which yielder lower odds ratios than the former). Nevertheless, results involving HRV were similar to the tabulated results. For example, a multivariate logistic regression model combining HR values and maximum Poincaré ratios was superior in performance over a model using HR alone, yielding odds ratios of 1.06 (95% CI, 1.02–1.12; $P = 0.002$) for mean HR (per beats per minute increase) and 9.43 (95% CI, 1.68–76.7; $P = 0.011$) for maximum HRV ratio (per unit increase). Inclusion of the HRV ratio in the regression analyses showed that increasing the maximum Poincare ratio was associated with an increased risk for mortality and increased odds by nearly 10%. Similarly, ROC curves demonstrated better prediction for mortality and LSIs using HR and HRV (AUCs, 0.86 and 0.73, respectively) than using HR alone (AUCs, 0.79 and 0.57, respectively).

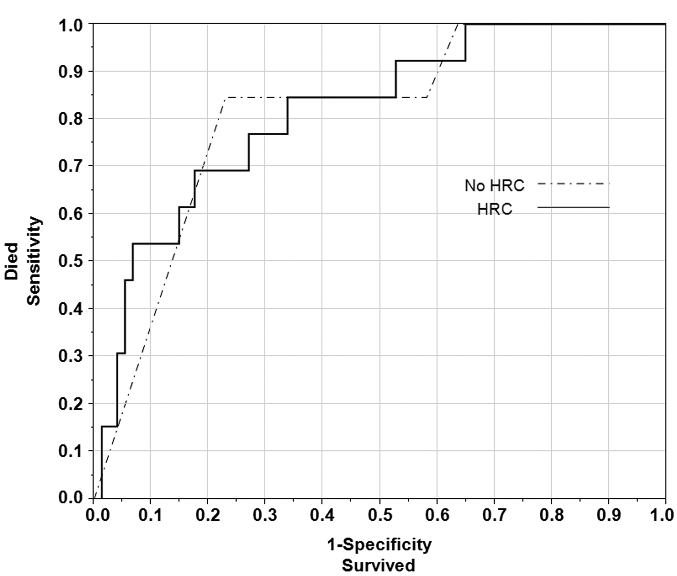

FIG. 3. **Receiver-operating characteristic curves for models predicting mortality (including GCS scores)**. Receiver-operating characteristic curves were obtained to examine the discriminating power of multivariate logistic regression models (including GCS scores) for the outcome of mortality in 108 subjects. The curves demonstrated better mortality prediction for models using vital signs, GCS scores, and HRC (AUC, 0.82) than for models using only GCS scores (AUC, 0.81).

In addition to the aforementioned notes, it is important to point out that models using and not using total GCS scores were considered separately in this study because GCS scores are not always available or practical to obtain in prehospital and battlefield environments. Like previous work and results described in Liu et al. (2), this study showed that models not using GCS scores were still able to predict mortality and the need for LSIs with greater than 80% accuracy. By integrating other mechanisms for scoring injuries in a rapidly changing environment (8), it is possible to preclude use of GCS scores while increasing prediction accuracy.

Because HRV and HRC can be calculated rapidly and noninvasively (16, 20, 21), they may be leveraged with routine vital signs to help change the paradigm in prehospital care for the severely injured. With today's advances in monitoring technology, these parameters could be displayed simultaneously on one screen and used at the injury scene for risk stratification of mass casualties requiring air transport, such as casualties occurring on the battlefield or a major highway. In addition, standard and new vital signs could be used together for rapid

triage of prehospital patients (e.g., which facility or what level/role of care) or during transport to assist with timely and accurate administration of LSIs. Thus, these data could play a role in facilitating prehospital care and patient stabilization until further care at a facility is available.

Future studies may include indicators of numeric and waveform data quality to provide a more comprehensive model for predictions of outcomes in trauma patients as well as development of a novel prehospital score using standard vital signs, HRV, and HRC.

Limitations

This study had limitations that mirrored previous work (2). In addition, lengths of ECG waveforms were short, and no data were excluded regardless of noise in the captured waveforms. A third limitation was that manual verification of all R waves for 108 trauma patient ECGs was performed by 2 individuals having no background in cardiology. Fourth, this study did not consider analyses for examining the discriminating power of the models for the outcome of LSI needs resulting in mortality (i.e., patients who required LSIs and who eventually died after trauma). A strategy similar to this study could be applied to perform these analyses in the future. A fifth limitation of this study was that times of actual LSIs were not recorded and stored in the TV database (8). Hence, this study could not directly measure how new vital signs changed with LSIs in individual patients. Nevertheless, this limitation did not compromise the results of this study, since analyses involved extremes (minimum HRC value and maximum HRV ratio), thereby strengthening the potential usefulness of new vital signs for triage and risk stratification.

Here, it is worth clarifying the role of helicopter medical transport in possibly influencing this study's analyses as well as the limitations of HRV and HRC in the clinical settings. Assessment of breath sounds, bowel sounds, blood pressure by auscultation, and even verbal communications with the patient is greatly impaired during helicopter flight due to noise (5, 22). Furthermore, although state-of-the-art blood pressure monitors are in widespread use in air medical services, they may not always be reliable at low pressures (5). Since this study did not focus on blood pressures, aforementioned results were not compromised. Inherent in this study is the possibility of mechanical noise and human error corrupting segments in the ECG waveforms, which could have altered HRV and HRC calculations for analysis. In addition, several groups (23, 24) have reported that the application of HRV in clinical settings is limited by poor interindividual and intraindividual reproducibility. Nevertheless, their conclusions may not be applicable to all HRV or HRC measures and trends in these measures. The results of previous work (15) and this study have shown that even in the presence of noise, HRV and HRC may still be able to discriminate between patient groups and monitor patients over time. Furthermore, recent work has shown that HRC trends can be reproduced across subjects (25). However, like any vital sign, HRV or HRC alone may not provide a complete picture of patient status. Therefore, new vital signs such as HRV and HRC should be used in conjunction with standard vital signs and other parameters for improved utility (2).

In summary, this study showed that multivariate logistic regression models using vital signs, HRV, and HRC to predict mortality and the need to perform LSIs were superior in predictive performance over models using solely traditional vital signs. Improvements in the timely use and diagnostic accuracy of transportable vital signs monitors will require utility of traditional and new vital signs from the trauma patient cohort.

ACKNOWLEDGMENTS

The authors acknowledge the expertise, dedication, and professionalism of the Emergency Medical Services paramedics, nurses, and staff in Houston who performed the patient care; and Denise Hinds, Timothy Welch, and Jeannette Podbielski (the University of Texas Health Science Center in Houston, Texas). The authors also thank Corina Necsoiu and Kerfoot Walker III who performed the manual verification of all R waves for 108 trauma patient ECGs from the TV database.

REFERENCES

1. Butler FK: Tactical combat casualty care: update 2009. *J Trauma* 69:S10–S13, 2010.
2. Liu NT, Holcomb JB, Wade CE, Darrah MI, Salinas J: Utility of vital signs, heart-rate variability and complexity, and machine learning for identifying the need for life-saving interventions in trauma patients. *Shock* 42:108–114, 2014.
3. Pickering TG, Shimbo D, Hass D: Ambulatory blood-pressure monitoring. *N Engl J Med* 354:2368–2374, 2006.
4. Low RB, Martin D: Accuracy of blood pressure measurements made aboard helicopters. *Ann Emerg Med* 17:604–612, 1988.
5. Garner DC: Noise in medical helicopters. *JAMA* 266:515–516, 1991.
6. Jones DW, Appel LJ, Sheps SG, Roccella EJ, Lenfant C: Measuring blood pressure accurately: new and persistent challenges. *JAMA* 289:1027–1030, 2003.
7. Lovett PB, Buchwald JM, Sturmann K, Bijur P: The vexatious vital: Neither clinical measurements by nurses nor an electronic monitor provides accurate measurements of respiratory rate in triage. *Ann Emerg Med* 45:68–76, 2005.
8. Liu NT, Holcomb JB, Wade CE, Batchinsky AI, Cancio LC, Darrah MI, Salinas J: Development and validation of a machine learning algorithm and hybrid system to predict the need for life-saving interventions in trauma patients. *Med Biol Comput Eng* 52:193–203, 2014.
9. Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS: Heart rate variability: a review. *Med Bio Eng Comput* 44:1031–1051, 2006.
10. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability. Standards of measurement, physiological interpretation and clinical use. *Circulation* 93: 1043–1065, 1996.
11. Saul JP: Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. *News Physiol Sci* 5:32–37, 1990.
12. Batchinsky AI, Cooke WH, Kuusela T, Cancio LC: Loss of complexity characterizes the heart-rate response to experimental hemorrhagic shock in swine. *Crit Care Med* 35:519–525, 2007.
13. Batchinsky AI, Skinner J, Necsoiu C, Jordan BS, Weiss D, Cancio LC: New measures of heart-rate complexity: effect of chest trauma and hemorrhage. *J Trauma* 68:1178–1185, 2010.
14. Ryan ML, Thorson CH, Otero CA, Vu T, Proctor KG: Clinical applications of heart rate variability in the triage and assessment of traumatically injured patients. *Anesthesiol Res Pract* 2011:416590, 2011.
15. Liu NT, Batchinsky AI, Cancio LC, Salinas J: The impact of noise on the reliability of heart-rate variability and complexity analysis in trauma patients. *Comput Biol Med* 43:1955–1964, 2013.
16. Liu NT, Cancio LC, Salinas J, Batchinsky AI: Reliable real-time calculation of heart-rate complexity in critically ill patients using multiple noisy waveform sources. *J Clin Monit Comput* 28:123–131, 2014.
17. Liu NT, Batchinsky AI, Cancio LC, Baker WL, Salinas J: Development and validation of a novel fusion algorithm for continuous, accurate, and automated R-wave detection and calculation of signal-derived metrics. *J Crit Care* 28:885.e9–885.e18, 2013.
18. Brennan M, Palaniswami M, Kamen P: Do existing measures of Poincarè plot geometry reflect nonlinear features of heart rate variability? *IEEE Trans Biomed Eng* 48:1342–1347, 2001.

19. Richman JS, Moorman JR: Physiological time series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol* 278: H2039–H2049, 2000.
20. Batchinsky AL, Salinas J, Kuusela T, Necsoiu C, Jones J, Cancio LC: Rapid prediction of trauma patient survival by analysis of heart rate complexity: impact of reducing data set size. *Shock* 32:565–571, 2009.
21. Clemens MG: The data sets needed for analysis of heart-rate complexity to identify trauma patients with potentially lethal injuries. *Shock* 33:1–2, 2010.
22. Hunt RC, Bryan DM, Brinkley VS, Whitley TW, Benson NH: Inability to assess breath sounds during air medical transport by helicopter. *JAMA* 265(15): 1982–1984, 1991.
23. Rickards CA, Ryan KL, Ludwig DA, Convertino VA: Is heart period variability associated with the administration of lifesaving interventions in individual prehospital trauma patients with normal standard vital signs? *Crit Care Med* 38:1666–1673, 2010.
24. Ryan KL, Rickards CA, Ludwig DA, Convertino VA: Tracking central hypovolemia with ECG in humans: cautions for the use of heart period variability in patient monitoring. *Shock* 33:583–589, 2010.
25. Liu NT, Kramer GC, Khan MN, Kinsky MP, Salinas J: Is heart-rate complexity a surrogate measure of cardiac output before, during, and after hemorrhage in a conscious sheep model of multiple hemorrhages and resuscitation? *J Trauma Acute Care Surg* (in press).